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Delays in the diagnostic pathways for primary pulmonary carcinoma in Southern Norway[☆]

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Summary

Background: This study intends to evaluate the delays in the diagnostic pathways for primary lung cancer in Southern Norway, and to compare results with recommendations from the British Thoracic Society (BTS) and the Swedish Lung Cancer Group (SLCG).

Design: A questionnaire-based prospective study of all patients diagnosed with primary lung cancer in Southern Norway from June 14, 2002 to June 13, 2005.

Results: Half of the 479 patients were referred to a specialist in pulmonology within 3 weeks (median) of first seeing their doctor concerning symptoms of malignant pulmonary disease. 71% of patients were seen by pulmonologist within 1 week of received referral, and not 100% as proposed by the BTS. 52% of the patients were diagnosed and informed of their disease within 2 weeks (BTS recommend 100%) of having received the referral letter, and 68% within 3 weeks (SLCG recommend 80%). 62% started treatment within 1 month of first contact with pulmonologist (SLCG 80%).

Conclusion: The delays in diagnosing lung cancer in the Agder region were within BTS and Swedish recommendations in 52–71% of cases. Although our results show good standings compared to other studies, the potential improvements for both the referring GP and the specialist investigators are discussed.

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Introduction

Primary lung cancer is the most important cause of cancer-related mortality in the Western world today. The same accounts for Norway, and the incidence is still increasing. The Agder counties in Southern Norway have, for partially unknown reasons, a higher incidence than Norway at large (The Norwegian Cancer Registry, 2005). For example, the incidence of primary lung cancer has almost doubled among

women in Eastern Agder from 1985 to 1995.¹ Agder serves 260 000 inhabitants. Thus, about 170 new cases of primary lung cancer are diagnosed in this area each year, where two main hospitals treat persons with these conditions, i.e. Sorlandet Sykehus Kristiansand (SSK) and Sorlandet Sykehus Arendal (SSA), offering all regular kinds of tumour-reducing treatments, including radiotherapy.

Although the overall prognosis for primary lung cancer is poor, with a mean survival of less than a year, rapid diagnosis and assessment are important to determine operability, suitability for radiotherapy, chemotherapy or palliative interventions, and to minimise the anxieties of patients and their families. The British Thoracic Society (BTS) and the Swedish Lung Cancer Group (SLCG) have therefore made recommendations concerning time limits for diagnosing lung cancer.²⁻⁴ Such recommendations are absent in Norway.

We thus intended to evaluate whether our clinics keep within the Swedish and the British time suggestions, and reveal needs for improvement to reduce delays in the diagnostic pathways. A Pub Med search for articles from Western Europe and North America on delays in the diagnostic process of lung cancer, shows that several studies have assessed delays for patients undergoing surgery, but studies are mostly retrospective.⁵⁻⁸ In a review article, Jensen et al.⁹ comment that selection bias can be considerable in studies on patients recruited from surgical or oncological departments, as these never include patients with known late-stage disease. During the last decade, only two smaller studies by Koyi et al.¹⁰ ($n = 134$) and Deegan et al.¹¹ ($n = 92$) have prospectively examined the various patient-, doctor- and hospital delays in the diagnosis and treatment of all mainstream non-selected lung cancer patients.

Methods

All patients diagnosed with primary lung cancer in Southern Norway, i.e. the Agder counties (Aust-Agder and Vest-Agder), were included in this prospective study between June 14, 2002 and June 13, 2005. After signing a written informed consent, a questionnaire, especially made for the study, concerning start of cancer-related symptoms and first date of contacting their doctor about these symptoms, was answered. For those patients who did not recall exact date of first symptom or first contact with doctor, only as "the beginning of", "the end of" or "the midst of month", this was transformed into the 1st, the 30th or the 15th of the actual month. If only the month was remembered, the protocol stated to record it as the 15th. Patients answering questionnaires from their home address were, in case of delayed replies, repeatedly (at least twice) reminded by telephone and/or mail. Physical status rating according to Eastern Cooperative Oncology Group (ECOG) Performance Status were noted for those who were too ill to answer these questionnaires.¹² If not able to sign the informed consent, an allowance to use basic medical information from the journal was attained by oral consent from patients or relatives. Relatives were occasionally able to answer some baseline questions concerning symptom start, doctor visits, smoking, etc.

Dated referral from general practitioner or other hospital wards, as well as date of referral receipt in the clinic, were collected as soon as possible after the first contact with the lung department. All definitions of delays used in this article were:

- *Patient delay*: Time from first symptom to first personal contact with doctor.
- *GP delay*: Time from first contact with general practitioner (GP) to date on written referral.
- *Referral delay*: Time from dated referral receipt to first contact with pulmonary consultant.
- *Specialist delay*: Time from first contact with pulmonary consultant to dated diagnostic histology/cytology.
- *Informed diagnostic delay*: Time from decision of doing a diagnostic procedure to informing patient of diagnosis. Time from decision was stated as the date of referral receipt+2 days, which is considered the mean time used (including weekends and public holidays) before a decision of diagnostic procedure/sequence was done.
- *Hospital delay*: Time from first contact with pulmonary consultant to start of treatment.
- *Total delay*: Time from first symptom to start of treatment.

Patients presenting with metastases in other organs, thereby being diagnosed before referred to a pulmonary consultant, were excluded from statistical analyses on delays, since our main goal was to investigate delays in our common diagnostic pathways. If those had been included in the analyses, diagnostic delays would have been incorrectly shortened, thereby introducing a selection bias for the main purpose of the study.

Medical information about histology and staging according to C. Mountain's revision in the International System for staging of lung cancer (TNM-stage) of disease and treatment,¹³ were collected from the patients' hospital records. Histology was classified according to the revised WHO classification of October 10, 1998.^{14,15} For those without histology, date of clinical decision was chosen as diagnostic date.

Because the BTS recommendations² principally concern the process of patient care, most of them represent considered clinical opinion, compatible with what evidence there is, and are not recommendations based just upon published scientific evidence.

The BTS recommendations of interest for our study state that:

- Patients referred by general practitioners, who have obvious clinical evidence of lung cancer, should be seen within 1 week of referral receipt in a respiratory physician's clinic, i.e. Referral delay.
- Regarding the confirmation of the diagnosis:
- The results of bronchoscopy or any other similar diagnostic test, including the histological or cytological result, should be available and communicated to the patient within 2 weeks of a decision to do it, i.e. Informed diagnostic delay.
- The recommendations from the Swedish Lung Cancer Study Group³ state that 80% of patients with:

- suspected lung cancer should wait no more than 1 week before they are investigated by a specialist, i.e. Referral delay.
- diagnosed lung cancer should wait no more than 3 weeks since first specialist investigation to a treatment decision is made and no more than 10 days from a treatment decision was made until start of treatment, summarised as Hospital delay.

Our local standard at the start of the study was that patients referred with a suspicion of lung cancer, should be investigated within 2 weeks.

The two hospitals were compared to look for differences in delays related to the diagnostic process. Age, gender and hospital (SSA versus SSK) were chosen as explanatory variables affecting delays in the multiple logistic regression analyses. Further, the histological class, i.e. small cell lung cancer (SCLC) versus non-small cell lung cancer (NSCLC), was chosen since SCLC grow and disseminate earlier than NSCLC, and thus give early symptoms. Myrdal et al.¹⁶ found more pronounced interaction between short delay and poor prognosis in patients with advanced tumour stage.

We also wanted to evaluate whether radiology before referral to the chest clinic could influence the GP or specialist delays. Main diagnostic procedure leading to the diagnosis was noted and compared between the two hospitals.

Statistical methods

Statistical descriptive analyses were performed with SPSS 13 (Statistical package for Social Sciences, SPSS Inc., Chicago, USA). All days recorded include weekends and public holidays. Continuous data were, when non-normally distributed, as judged by measures of dispersion (*sd*) and/or bar charts, and, when in doubt, by Lilliefors' test for skewedness, analysed with non-parametric tests, such as Mann-Whitney *U*-test. Skewed data are shown with the median value as a measure of central tendency and with the interquartile range (IQR, i.e. 25th and 75th percentiles) as the measure of dispersion. Normally distributed data were evaluated with *t*-test. The corresponding central tendency

and dispersion values are displayed as mean and standard deviation (*sd*), respectively. Proportions were analysed with χ^2 -tests. Extreme values, judged as definite outliers, were extracted from analyses. Differences were considered statistically significant with an alpha below 0.05 ($P < 0.05$), two-sided test. Data on delays also showed skewed distribution. Hence, data were transformed into categorical variables with a cut-off at 21 days for all delays, except referral delay (cut-off at 7 days). Multiple logistic regression analyses on delays were then run with backward stepwise conditional methods, testing for the following categorical variables: Age (cut-off: ≤ 70 years = 0, > 70 years = 1), gender (men = 0, female = 1), ECOG performance status (status 0–2 = 0 and 3–4 = 1), TNM stage (stage 1a–3a = 0 and 3b–4 = 1), histology (NSCLC = 0 and SCLC = 1), clinic (SSK = 0 and SSA = 1), and whether X-ray or CT scan of the chest was required by referring doctor or not (radiology before referral = 0 and not = 1).

Proportional differences between our results and BTS and SLCG recommendations were tested through χ^2 -tests in Sample Power (Sample Power, SPSS Corp., Chicago, USA), assuming a sample size of 470 patients and with a power of above 90%, two sided test.

Results

Of 492 eligible patients, 479 patients were successively enrolled over a 3-year period, i.e. an inclusion rate of 97% (see Fig. 1). 18% of patients were too ill to answer questionnaires at the time of diagnosis, already being in very poor condition by the time diagnosis was established due to for example sequela after cerebral thrombus, extreme fatigue or depression. It seems important to include these patients in the study, as they represent the sickest, often those with long pre-hospital delays, and requiring either palliative radiotherapy or best supportive care only.

Another 7.5% ($n = 36$) were diagnosed at the time of death or by autopsy. 75% of questionnaires regarding delays were answered in the clinic, while the rest were answered at home and mailed. The mean age was 67 for women and 68

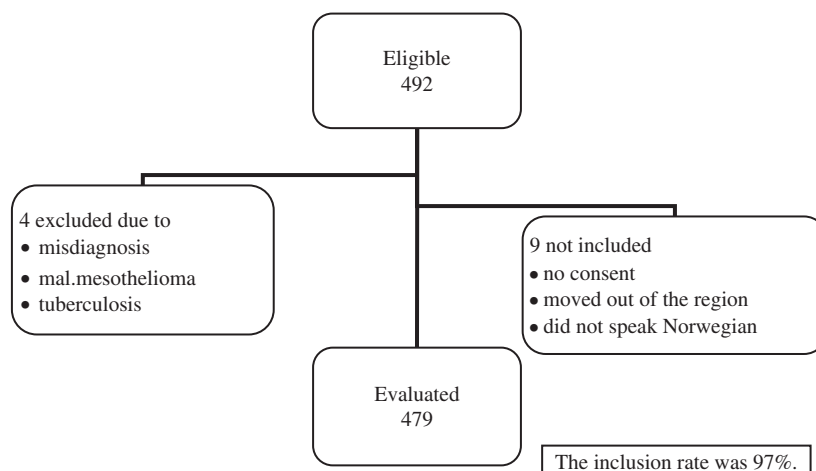


Figure 1 Eligible, excluded, not included and evaluated patients.

Table 1 Baseline characteristics for primary lung cancer in Agder counties, Southern Norway.

	(n) Unless stated differently
Age: yr, mean (SD)	68 (11)
Sex, females	42 (199)
Current smokers	47 (227)
Histology	
SCLC	21 (102)
Adenocarcinoma	33 (157)
Squamous cell ca.	25 (113)
Large cell/undifferentiated	12 (59)
No histological diagnosis	10 (48)
TNM stage (Mountain)	
Ia	8 (37)
Ib	8 (36)
IIa–IIb	4 (21)
IIIa	8 (40)
IIIb	23 (109)
IV	49 (235)
Performance status (ECOG)	
0	14 (65)
1	33 (160)
2	8 (86)
3	22 (106)
4	11 (52)

N = 479.

SCLC = small cell lung cancer.

TNM = tumour node metastasis staging of lung cancer, according to Mountain's revised classification.¹³ Stages IIIb and IV are advanced cancer, not leaving chance of being cured. Performance stage according to Eastern Cooperative Oncology Group/World Health Organization.¹²

for men. 95% had a positive smoking history (smokers and ex-smokers), half of the patients still smoking (Table 1).

More than two-thirds (72%) of patients were in advanced, non-operable stage of lung cancer and half of them had distant metastases (stage IV) at the time of diagnosis. One in five was diagnosed with SCLC and seven in ten with NSCLC.

Median and mean patient delays were approximately 3 weeks and 3 months, respectively, thereby revealing the considerably skewed distribution of data (Table 2 and Fig. 2).

Half of the patients contacted their doctor within 3 weeks after their first cancer-related symptom. The general practitioner delay was at large comparable to the patient delay, being somewhat lower, though not statistically significant, for the mean value (66 versus 79 days, $P = 0.80$). 88% were seen by a pulmonary consultant within 2 weeks of referral receipt (Fig. 3, Referral delay), the median being 1 day (IQR: 0–7). Most of those who waited longer, had either imprecise information or another diagnosis, without a suspicion of malignancy, in the referral letter.

71% of patients experienced a referral delay of less than 1 week, in comparison to the BTS recommendation proposing all (100%) patients to be investigated within a week ($P < 0.001$, χ^2 -test). The corresponding proportion in the Swedish guidelines were 80% ($P = 0.05$). Half of the patients were diagnosed and informed within 2 weeks, according to the British recommendations (52% vs. 100%, $P < 0.001$), and two-thirds within 3 weeks, as suggested by the Swedish recommendations (68% vs. 80%, $P < 0.01$). Patients were informed 1 (median) day (IQR: 0–5) after dated histological/cytological diagnosis. For patients receiving active, tumour-reducing treatment ($n = 311$), another 13 (median) days (IQR: 4–23) passed before treatment was initiated. 62% of these patients were diagnosed and had treatment started within 31 days, not 80% as proposed by the Swedes ($P < 0.01$). Median total delay was just below 4 months.

3/4 of patients had chest X-ray performed before they were referred to a pulmonary consultant. Although the GP delay thereby seemed somewhat shortened in multivariate analyses, an X-ray prior to referral to pulmonologist did not affect the delay from GP to final diagnosis.

Advanced ECOG performance status and advanced TNM stage reduced referral delay with statistical significance, with a halved odds ratio (0.49 and 0.48 with a 95% CI 0.27–0.90 and 0.28–0.80, respectively). Advanced TNM classification also reduced specialist-delay (OR 0.45, 95% CI 0.25–0.79), informed diagnostic delay (OR 0.42, 95% CI 0.25–0.68) as well as hospital delay (OR 0.43, 95% CI 0.24–0.78).

Female gender (OR 0.51, 95% CI 0.29–0.91) was associated with shorter specialist delay. SCLC also had a definitely shorter hospital delay than NSCLC (OR 0.29, 95% CI 0.16–0.53).

Specialist delay was longer at SSA (11, median, IQR 7–18) than at SSK (8, 3–21), $P < 0.004$. The corresponding values for informed diagnostic delay were 17 (10–25) at SSA versus 12 (5–25) at SSK, $P < 0.002$. Time from receiving diagnosis to informing the patient was 1 day (median, IQR 0–4) at SSK compared to 3 (0–7) at SSA, $P < 0.0001$.

Discussion

71% of patients with a suspicion of primary lung cancer experienced a "Referral delay" of less than 1 week in the Agder region, Norway, while the BTS and Swedish recommendations propose 100% or 80% of patients, respectively, to be within suggested time limits. The corresponding proportions for "Informed diagnostic delay" were 52% within 2 weeks and 68% within 3 weeks, respectively. 62% of patients experienced a "Hospital delay" of less than 31 days. We thus, in comparison with international recommendations, uncover a considerable potential for improvement in the diagnostic pathways of lung cancer in this region.

A shortcoming of our study might be that only 75% answered the baseline questionnaires themselves. Hence, when patients were not able to answer the questions themselves, efforts were made in collecting detailed information from relatives. Nevertheless, some uncertainty and selection bias might have been introduced here. However, another comparable, although retrospective, study did not include patients who were offered best

Table 2 Delays in the diagnostic pathway for primary lung cancer in Southern Norway.

	N	Days		< 3 weeks (%)	BTS recommendations	Swedish recommendations
		Median (IQR)	Mean (SD)			
Patient delay	376	19 (2–77)	79 (179)	51		
GP delay	404	22 (4–61)	66 (143)	50		
Referral delay	463	1 (0–7)	6 (17)	95	Within 1 week 71%	within 1 week 71%
Specialist delay	448	8 (3–19)	17 (30)	82		
Informed diagnostic delay	441	14 (6–25)	25 (37)	68	Within 2 weeks 52%	Within 3 weeks 68%
Hospital delay	310	25 (13–42)	35 (36)	44		Within 31 days 62%
Total delay	273	118 (68–220)	219 (313)	2		

N = 479.

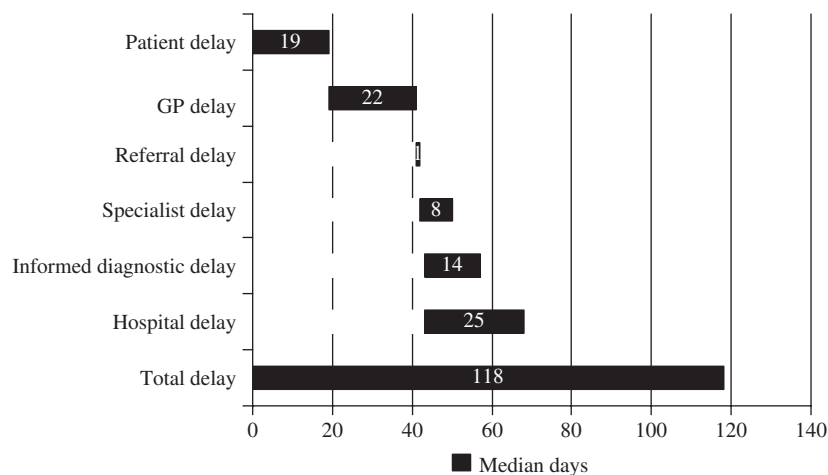
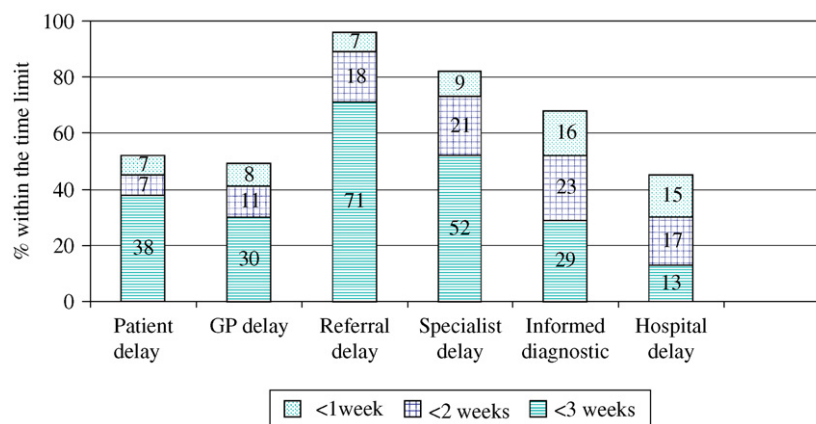
Definitions: see text.

The Swedish recommendations³ recommend 80% of patients to experience a

- referral delay within 7 days
- hospital delay within 31 days

The BTS recommendations² advice

- referral delay no more than 1 week
- information to the patient about histology/cytology should be within 2 weeks of the decision to do the diagnostic procedure

**Figure 2** Delays (median) in the diagnostic process of primary pulmonary carcinoma, Southern Norway, 2002–2005.**Figure 3** Delays in the diagnosis of primary pulmonary carcinoma within 1, 2 and 3 weeks.

supportive care only.¹⁶ By also including those patients who were offered only best supportive care, thereby to a larger extent those with an advanced disease stage and low performance status as well as more elderly persons, data will involuntarily be more imperfect. Since most patients had a smoking history and thereby many patients already suffered from COPD or cardiovascular disease, with cough and dyspnoea as common symptoms, one could argue that this might influence both the patient and referral delays. However, we have no data available to investigate these interactions more thoroughly.

Salomaa et al.¹⁷ also included those offered best supportive care (132 patients). Both "Patient (14 days, median) and GP delay" (16 days) seemed slightly shorter in Salomaa's study, compared to our study (19 and 22 days, respectively), while "Specialist delay" in our study seemed shorter (8 versus 15 days). Specialist delay is of course of greatest importance in our study, since it reveals our clinical results directly. Thus, although our results may not fulfil BTS and Swedish recommendations, they seem somewhat better than the only comparable study from Finland regarding specialist handling. We thus believe that we, considering the non-selected patient population, both present results with a sound validity and also relatively good values.

In our opinion, the Swedish recommendations, where 80% of patients should experience to be within the suggested time limits, seem more realistic than the British. Regarding "Referral delay" we have results close to the Swedish recommendations. We believe "Referral delay" could be shortened if referring physicians are encouraged to make telephone calls or telefax referrals instead of writing letters of referral. This delay could of course also be shortened if some referring physicians improve their information with a clearer suspicion of lung cancer in their referring letters.

"Informed diagnostic delay" could also be shortened by several manoeuvres. First, it will be looked at whether changes in first choice of diagnostic procedures could establish the diagnosis more quickly. Second, the time to first diagnostic procedure might also be shortened if given higher priority and converted to improved hospital logistics. Third, the delay from established morphological diagnosis to informing patients could probably also be shortened by approximately 1 day, although many specialists would consider our delay of 2 days already to be very efficient indeed.

For "Specialist delay" the median time from first investigation at hospital to established histological diagnosis was 8 days, the mean being 17 days. Thus, the diagnostic process lasts too long for some patients. Multidisciplinary team meetings are held once a week. Possible diagnostic procedures are discussed if assistance from radiologist or surgeon is considered necessary. Otherwise, treatment is discussed after histological diagnosis is established. Some times this is discussed after the patient has been informed, at other times before-, depending on whether line of treatment seems debatable.

More than two-thirds of patients were already in advanced tumour stage at time of diagnosis (stages IIIb and IV). This is a higher proportion than in most other studies. This could have several reasons. First, since this study included all patients, not only those receiving tumour reducing treatments, more advanced cancers would natu-

rally be included, giving higher proportions of patients with advanced cancer. Second, the diagnostic standards were adequate and updated, thereby resulting in a higher precision in TNM classification than in most previous studies. Third, there was a relatively high proportion of females in the studied population, as already known from previous data from the Norwegian Cancer Registry. But whether this should partly explain a high proportion of advanced cancer stages, we are not able to answer. Fourth, as many of these patients have serious comorbidity, such as COPD, they seem to tolerate a large extent of symptoms before they or their GP realise that there is need for further investigations. The advanced stage is partly why many were too ill to answer questionnaires, being weakened by fatigue or nausea.

Interestingly, whether X-ray or CT scan of the chest were done before referral to specialist or not, did not influence the total time to diagnosis.

The multivariate logistic regression analysis showed that especially patients with advanced tumour stage, but also poor performance status, had a higher probability of a short referral delay. One might expect these patients to have waited longer before contacting their GP, thus presenting with a heavy symptom load. However, a longer "Patient delay" was not evident for these patients compared to those with less advanced disease. An explanation could be the multi-morbidity for many of those patients, with for example previous experiences of daily cough, sputum and recurrent lower airway infections. We have no information to what extent patients supersede symptoms in this survey. An advanced TNM classification was also associated with shorter "Specialist, Informed diagnostic and Hospital delays". This is most probably due to more easily accessible tumour masses for biopsy in advanced disease, and a greater need for rapid, symptom-related treatment than in less advanced disease.

SCLC is associated with a shorter time from established diagnosis to start of treatment (i.e. reduced "hospital delay", but not "Specialist delay" or "Informed diagnostic delay"), compared to NSCLC. This is most probably due to the rapid onset chemotherapy for a high proportion of patients with SCLC. Persons with NSCLC are to a much larger extent referred to surgery or radiation as first line treatment, thereby including administrative delays not experienced with our in-department chemotherapy.

The basis for this study was to find areas for enhancement in the diagnostic procedure. The results revealed important shortcomings and a basis for improvement. In this process, a comparison of the two hospitals also revealed differences in the diagnostic logistics of local interest, giving both hospitals ideas on how to increase the efficiency of the diagnostic processes. Both hospitals have after the study changed routines to improve their standards, e.g. such as handling referrals more efficiently. We thus believe that similar registrations profitably could be introduced in other hospitals to reveal shortcomings and improve standards.

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